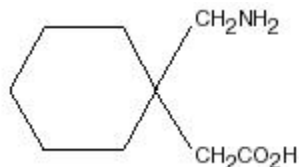


## GABAPENTIN - gabapentin capsule

IVAX Pharmaceuticals, Inc.

### DESCRIPTION

Gabapentin is an anticonvulsant for oral administration. It is chemically designated as 1- (aminomethyl) cyclohexanecarboxylic acid. Gabapentin is a white to off-white crystalline solid with a  $pK_{a1}$  of 3.7 and a  $pK_{a2}$  of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25. It has the following structural formula:



$C_9H_{17}NO_2$  M.W. 171.24

Each gabapentin capsule, for oral administration, contains 100 mg, 300 mg or 400 mg of gabapentin and contains the following inactive ingredients: black iron oxide, corn starch, gelatin, lactose monohydrate, talc and titanium dioxide. In addition, the 300 mg contains D&C yellow #10 and D&C red #33, and the 400 mg contains red and yellow iron oxide.

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify  $GABA_A$  or  $GABA_B$  radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100  $\mu M$  and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, *N*-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine,  $\alpha 1$ ,  $\alpha 2$ , or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate  $\mu$ , delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20- $\alpha$ -benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

*In vitro* studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

#### Pharmacokinetics and Drug Metabolism

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

##### Oral Bioavailability

Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and  $C_{max}$ ).

##### Distribution

Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is  $58 \pm 6$  L (Mean  $\pm$  SD). In patients with epilepsy, steady-state predose ( $C_{min}$ ) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

##### Elimination

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see *Special Populations, Patients*

with *Renal Insufficiency*, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see **DOSAGE AND ADMINISTRATION, Table 3**).

#### Special Populations

##### Adult patients with renal insufficiency

Subjects ( $N=60$ ) with renal insufficiency (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance  $>60$  mL/min) to 52 hours (creatinine clearance  $<30$  mL/min) and gabapentin renal clearance from about 90 mL/min ( $>60$  mL/min group) to about 10 mL/min ( $<30$  mL/min). Mean plasma clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min.

Dosage adjustment in adult patients with compromised renal function is necessary (see **DOSAGE AND ADMINISTRATION**). Pediatric patients with renal insufficiency have not been studied.

##### Hemodialysis

In a study in anuric adult subjects ( $N=11$ ), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (see **DOSAGE AND ADMINISTRATION**).

##### Hepatic disease

Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

##### Age

The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CL<sub>r</sub>) and CL<sub>r</sub> adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function. (See **PRECAUTIONS, Geriatric Use**, and **DOSAGE AND ADMINISTRATION**.)

##### Pediatric

Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and  $<5$  years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10 to 65 mg/kg/day given TID. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children  $<5$  years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants  $<1$  year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day (see **DOSAGE AND ADMINISTRATION**).

##### Gender

Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

##### Race

Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

## Clinical Studies

### Epilepsy

The effectiveness of gabapentin as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in some studies) seizures per month, gabapentin or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as  $(T - B)/(T + B)$ , where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared gabapentin 1200 mg/day divided TID with placebo. Responder rate was 23% (14/61) in the gabapentin group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the gabapentin group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily 1200 mg/day divided TID gabapentin ( $N=101$ ) with placebo ( $N=98$ ). Additional smaller gabapentin dosage groups (600 mg/day,  $N=53$ ; 1800 mg/day,  $N=54$ ) were also studied for information regarding dose response. Responder rate was higher in the gabapentin 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the gabapentin 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant ( $p=0.224$ ). A better response was seen in the gabapentin 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared gabapentin 900 mg/day divided TID ( $N=111$ ) and placebo ( $N=109$ ). An additional gabapentin 1200 mg/day dosage group ( $N=52$ ) provided dose-response data. A statistically significant difference in responder rate was seen in the gabapentin 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the gabapentin 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day gabapentin (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of gabapentin on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic-clonic seizure in either the baseline or in the treatment period in all three placebo-controlled studies were included in these analyses. There were several response ratio comparisons that showed a statistically significant advantage for gabapentin compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses ( $N=162$ , gabapentin;  $N=89$ , placebo) also showed a significant advantage for gabapentin over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of gabapentin was used. Within each study the results did not show a consistently increased response to dose. However, looking across studies, a trend toward increasing efficacy with increasing dose is evident (see Figure 1).

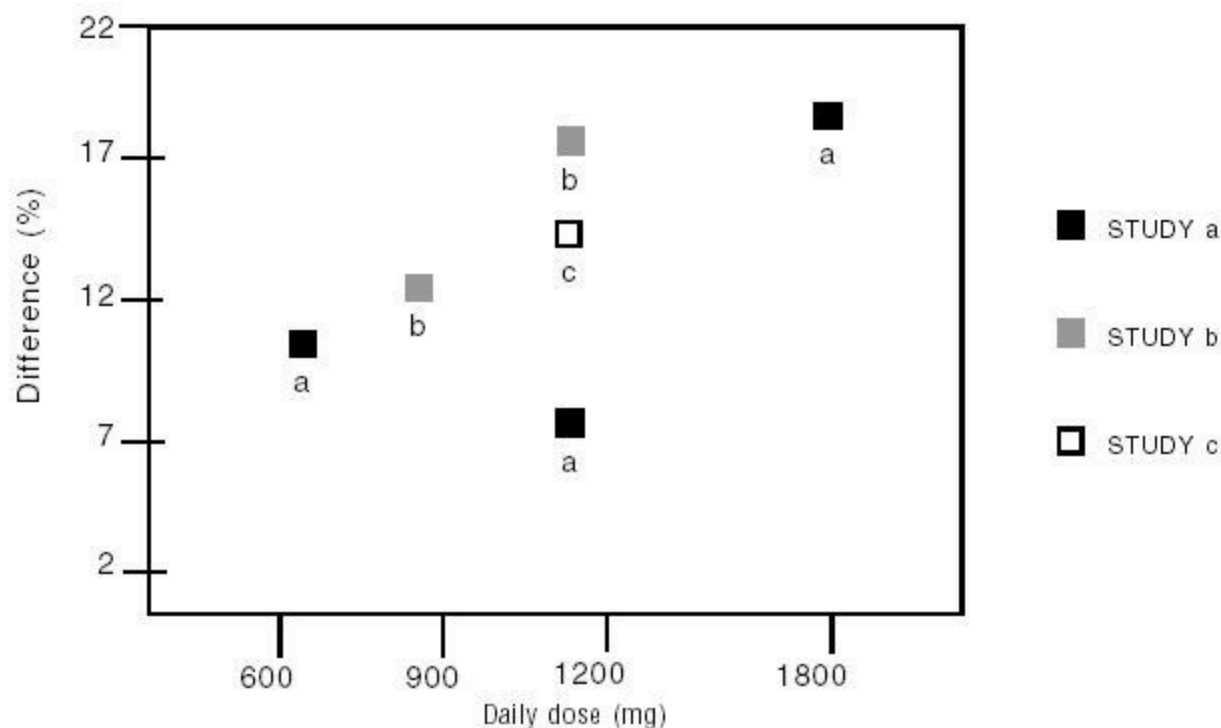


FIGURE 1. Responder Rate in Patients Receiving Gabapentin Expressed as a Difference from Placebo by Dose and Study: Adjunctive Therapy Studies in Patients  $\geq 12$  Years of Age With Partial Seizures.

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from clinical trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern indicating that age had any effect on the response to gabapentin. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy among racial groups. A fourth study in pediatric patients age 3 to 12 years compared 25 - 35 mg/kg/day gabapentin (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the response ratio was statistically significantly better for the gabapentin group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for gabapentin (21%) was not significantly different from placebo (18%). A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day gabapentin (N=38) with placebo (N=38) in patients who were receiving at least one marketed antiepileptic drug and had at least one partial seizure during the screening period (within 2 weeks prior to baseline). Patients had up to 48 hours of baseline and up to 72 hours of double-blind video EEG monitoring to record and count the occurrence of seizures. There were no statistically significant differences between treatments in either the response ratio or responder rate.

## INDICATIONS AND USAGE

### Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Gabapentin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 - 12 years.

## CONTRAINDICATIONS

Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

## WARNINGS

### Neuropsychiatric Adverse Events

Pediatric Patients 3 – 12 years of age

Gabapentin use in pediatric patients with epilepsy 3 - 12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily

behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3 - 12 years of age, the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs. 1.3% (placebo-treated patients); hostility 5.2% vs. 1.3%; hyperkinesia 4.7% vs. 2.9%; and thought disorder 1.7% vs. 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

### **Withdrawal Precipitated Seizure, Status Epilepticus**

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving gabapentin was 0.6% (3 of 543) vs. 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with gabapentin across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with gabapentin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with gabapentin.

### **Tumorigenic Potential**

In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. (See **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility.**) The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and pre-existing tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

### **Sudden and Unexplained Death in Patients with Epilepsy**

During the course of premarketing development of gabapentin 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the gabapentin program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the gabapentin cohort and the accuracy of the estimates provided.

## **PRECAUTIONS**

### **Information for Patients**

Patients should be instructed to take gabapentin only as prescribed. Patients should be advised that gabapentin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (see **Drug Interactions**).

### **Laboratory Tests**

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. The value of monitoring gabapentin blood concentrations has not been established. Gabapentin may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

### **Drug Interactions**

*In vitro* studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mcg/mL; 1 mM)

was a slight degree of inhibition (14%-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the  $C_{max}$  at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs. The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

#### Phenytoin

In a single (400 mg) and multiple dose (400 mg TID) study of gabapentin in epileptic patients ( $N=8$ ) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

#### Carbamazepine

Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg TID;  $N=12$ ) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

#### Valproic Acid

The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg TID;  $N=17$ ) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

#### Phenobarbital

Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg TID;  $N=12$ ) are identical whether the drugs are administered alone or together.

#### Naproxen

Coadministration ( $N=18$ ) of naproxen sodium capsules (250 mg) with gabapentin (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin had no effect on naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

#### Hydrocodone

Coadministration of gabapentin (125 to 500 mg;  $N=48$ ) decreases hydrocodone (10 mg;  $N=50$ )  $C_{max}$  and AUC values in a dose-dependent manner relative to administration of hydrocodone alone;  $C_{max}$  and AUC values are 3% to 4% lower, respectively, after administration of 125 mg gabapentin and 21% to 22% lower, respectively, after administration of 500 mg gabapentin. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

#### Morphine

A literature article reported that when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule ( $N=12$ ), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see **PRECAUTIONS**). Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The magnitude of interaction at other doses is not known.

#### Cimetidine

In the presence of cimetidine at 300 mg q.i.d. ( $N=12$ ) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

#### Oral Contraceptives

Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg TID;  $N=13$ ). The  $C_{max}$  of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

#### Antacid (Aluminum Hydroxide and Magnesium Hydroxide)

Aluminum hydroxide and magnesium hydroxide reduced the bioavailability of gabapentin ( $N=16$ ) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after aluminum hydroxide and magnesium hydroxide. It is recommended that gabapentin be taken at least 2 hours following aluminum hydroxide and magnesium hydroxide administration.

### Effect of Probenecid

Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

### Drug/Laboratory Tests Interactions

Because false positive readings were reported with the Ames N-Multistix SG<sup>®</sup> dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg per day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear. Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on an mg/m<sup>2</sup> basis).

### Pregnancy

#### Pregnancy Category C

Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m<sup>2</sup> basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m<sup>2</sup> basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m<sup>2</sup> basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m<sup>2</sup> basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m<sup>2</sup> basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m<sup>2</sup> basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m<sup>2</sup> basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Use in Nursing Mothers

Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, gabapentin should be used in women who are nursing only if the benefits clearly outweigh the risks.

## Pediatric Use

Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

## Geriatric Use

Clinical studies of gabapentin in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients (see **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION**).

## ADVERSE REACTIONS

### Epilepsy

The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus. The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility (see **WARNINGS, Neuropsychiatric Adverse Events**).

Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received gabapentin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

### Incidence in Controlled Clinical Trials

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when gabapentin was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 Years of Age (Events in at Least 1% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/Adverse Event	Gabapentin <sup>a</sup> N = 543%	Placebo <sup>a</sup> N = 378%
<b>Body As A Whole</b>		
Fatigue	11.0	5.0
Weight increase	2.9	1.6
Back pain	1.8	0.5
Peripheral edema	1.7	0.5
<b>Cardiovascular</b>		
Vasodilation	1.1	0.3
<b>Digestive System</b>		
Dyspepsia	2.2	0.5
Mouth or throat dry	1.7	0.5
Constipation	1.5	0.8
Dental abnormalities	1.5	0.3
Increased appetite	1.1	0.8



<b>Hematologic and Lymphatic Systems</b>		
Leukopenia	1.1	0.5
<b>Musculoskeletal System</b>		
Myalgia	2.0	1.9
Fracture	1.1	0.8
<b>Nervous System</b>		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination abnormal	1.1	0.3
<b>Respiratory System</b>		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
<b>Skin and Appendages</b>		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
<b>Urogenital System</b>		
Impotence	1.5	1.1
<b>Special Senses</b>		
Diplopia	5.9	1.9
Amblyopia <sup>b</sup>	4.2	1.1
<b>Laboratory Deviations</b>		
WBC decreased	1.1	0.5
<sup>a</sup> Plus background antiepileptic drug therapy <sup>b</sup> Amblyopia was often described as blurred vision		

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne. Among the treatment-emergent adverse events occurring at an incidence of at least 10% of gabapentin treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with gabapentin. The incidence of adverse events increased slightly with increasing age in patients treated with either gabapentin or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 2% of gabapentin-treated patients age 3 to 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. Adverse events were usually mild to moderate in intensity.

Table 2. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial (Events in at Least 2% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/Adverse Event	Gabapentin <sup>a</sup> N=119 %	Placebo <sup>a</sup> N=128 %
<u>Body As A Whole</u>		
Viral Infection	10.9	3.1
Fever	10.1	3.1
Weight Increase	3.4	0.8
Fatigue	3.4	1.6
<u>Digestive System</u>		
Nausea and/or Vomiting	8.4	7.0
<u>Nervous System</u>		
Somnolence	8.4	4.7
Hostility	7.6	2.3
Emotional Lability	4.2	1.6
Dizziness	2.5	1.6
Hyperkinesia	2.5	0.8
<u>Respiratory System</u>		
Bronchitis	3.4	0.8
Respiratory Infection	2.5	0.8
<sup>a</sup> Plus background antiepileptic drug therapy		

Other events in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

#### Other Adverse Events Observed During All Clinical Trials

##### Clinical Trials in Adults and Adolescents

Gabapentin has been administered to 2074 patients >12 years of age during all adjunctive therapy clinical trials in epilepsy, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to gabapentin who experienced an event of the type cited on at least one occasion while receiving gabapentin. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

##### Body as a whole

*Frequent:* asthenia, malaise, face edema

*Infrequent:* allergy, generalized edema, weight decrease, chill

*Rare:* strange feelings, lassitude, alcohol intolerance, hangover effect

##### Cardiovascular system

*Frequent:* hypertension

*Infrequent:* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur

*Rare:* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis

## Digestive system

*Frequent:* anorexia, flatulence, gingivitis

*Infrequent:* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly

*Rare:* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perlèche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm

## Endocrine system

*Rare:* hyperthyroid, hypothyroid, goiter, hypoenzyme, ovarian failure, epididymitis, swollen testicle, cushingoid appearance

## Hematologic and lymphatic system

*Frequent:* purpura most often described as bruises resulting from physical trauma

*Infrequent:* anemia, thrombocytopenia, lymphadenopathy

*Rare:* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased

## Musculoskeletal system

*Frequent:* arthralgia

*Infrequent:* tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test

*Rare:* costochondritis, osteoporosis, bursitis, contracture

## Nervous system

*Frequent:* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility

*Infrequent:* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis

*Rare:* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture

## Respiratory system

*Frequent:* pneumonia

*Infrequent:* epistaxis, dyspnea, apnea

*Rare:* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

## Dermatological

*Infrequent:* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex

*Rare:* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp, seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling

## Urogenital system

*Infrequent:* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal

*Rare:* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain

## Special senses

*Frequent:* abnormal vision

*Infrequent:* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness

*Rare:* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell

#### Clinical Trials in Pediatric Patients with Epilepsy

Adverse events occurring during epilepsy clinical trials in 449 pediatric patients 3 to 12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are:

**Body as a Whole:** dehydration, infectious mononucleosis

**Digestive System:** hepatitis

**Hemic and Lymphatic System:** coagulation defect

**Nervous System:** aura disappeared, occipital neuralgia

**Psychobiologic Function:** sleepwalking

**Respiratory System:** pseudocroup, hoarseness

#### Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, movement disorder, and Stevens-Johnson syndrome.

Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

#### DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of gabapentin has not been evaluated in human studies.

#### OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of gabapentin up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

#### DOSAGE AND ADMINISTRATION

Gabapentin is given orally with or without food.

If gabapentin dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week (a longer time period may be needed at the discretion of the prescriber).

#### Epilepsy

Gabapentin is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established.

#### Patients >12 Years of Age

The effective dose of gabapentin is 900 to 1800 mg/day and given in divided doses (three times a day) using 300 or 400 mg capsules, 600 or 800 mg tablets. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 or 400 mg capsules, or 600 or 800 mg tablets three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the TID schedule should not exceed 12 hours.

#### Pediatric Patients Age 3 – 12 years

The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of gabapentin in patients 5 years of age and older is 25-35 mg/kg/day and given

in divided doses (three times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (three times a day). (See **CLINICAL PHARMACOLOGY, Pediatrics**.) Gabapentin may be administered as the oral solution, capsule, or tablet, or using combinations of these formulations. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy.

Further, because there are no significant pharmacokinetic interactions among gabapentin and other commonly used antiepileptic drugs, the addition of gabapentin does not alter the plasma levels of these drugs appreciably.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

### DOSAGE IN RENAL IMPAIRMENT

Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance ( $C_{Cr}$ ) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females  $C_{Cr} = (0.85)(140 - \text{age})(\text{weight}) / [(72)(S_{Cr})]$

for males  $C_{Cr} = (140 - \text{age})(\text{weight}) / [(72)(S_{Cr})]$

where age is in years, weight is in kilograms and  $S_{Cr}$  is serum creatinine in mg/dL.

Dosage adjustment in patients  $\geq 12$  years of age with compromised renal function or undergoing hemodialysis is recommended as follows (see dosing recommendations above for effective doses in each indication).

TABLE 3. Gabapentin Dosage Based on Renal Function

Renal Function Creatinine Clearance(mL/ min)	Total Daily Dose Range(mg/day)	Dose Regimen(mg)				
$\geq 60$	900-3600	300 TID	400 TID	600 TID	800 TID	1200 TID
>30-59	400-1400	200 BID	300 BID	400 BID	500 BID	700 BID
>15-29	200-700	200 QD	300 QD	400 QD	500 QD	700 BID
15 <sup>a</sup>	100-300	100 QD	125 QD	150 QD	200 QD	300 QD
		Post-Hemodialysis Supplemental Dose (mg) <sup>b</sup>				
Hemodialysis		125 <sup>b</sup>	150 <sup>b</sup>	200 <sup>b</sup>	250 <sup>b</sup>	350 <sup>b</sup>

<sup>a</sup> For patients with creatinine clearance <15 mL/min, reduced daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

<sup>b</sup> Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

The use of gabapentin in patients <12 years of age with compromised renal function has not been studied.

### **Dosage in Elderly**

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

### **HOW SUPPLIED**

Gabapentin Capsules are available as white, opaque hard gelatin capsules, spin printed



“4381” on the cap and “100 mg” on the body containing 100 mg gabapentin packaged in bottles of 100, 500, 1000 and 4000 capsules and unit-dose boxes of 100 capsules.

Gabapentin Capsules are available as yellow opaque cap/white opaque body hard gelatin capsules, spin printed



“4382” on the cap and “300 mg” on the body containing 300 mg gabapentin packaged in bottles of 100, 500, 1000 and 2000 capsules and unit-dose boxes of 100 capsules.

Gabapentin Capsules are available as orange opaque cap/white opaque body hard gelatin capsules, spin printed



“4383” on the cap and “400 mg” on the body containing 400 mg gabapentin packaged in bottles of 100, 500, 1000 and 1500 capsules and unit-dose boxes of 100 capsules.

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

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